

REMARKS

Applicants respectfully request reconsideration of the application in view of the foregoing amendments and the following remarks. Claims 1 and 7 have been amended. Claims 3 and 9 have been cancelled. Thus, Claims 1, 2, and 4-8 are pending in the application. Support for the amendment to Claim 1 and Claim 7 may be found, for example, at page 9, lines 3 to 16 of the specification as filed. Thus, no new matter has been added. Reconsideration and withdrawal of the present rejections in view of the amendments and comments presented herein are respectfully requested. In response to the Office Action, Applicant respectfully requests the Examiner to reconsider the above-captioned application in view of the following comments.

Rejection of Claims 1 to 3 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1 to 3 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* (Chirality, 12:26-29, 2000) in view of Makarova *et al.* (Russian Journal of General Chemistry, 71(7):1126-1129, 2001). Specifically, the Examiner asserts that one of skill in the art would be motivated by the structure of the compound disclosed in Liu *et al.* to apply the teaching of Makarova *et al.* to the applicants β -aminovinyl ketone (e.g. (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine). However, as explained below, this combination of references would not render the claimed invention as obvious. As explained below, none of the cited references, even when combined would lead one of skill in the art to the process for producing an N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine by reducing a (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine in the presence of a carboxylic acid.

The Examiner states that Makarova *et al.* teaches a method of transforming structurally similar compound with NaBH₄ (sodium borohydride). However, Makarova *et al.* does not teach reduction of a β -aminovinyl ketone (e.g. (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine) in the presence of a carboxylic acid. Additionally, the Examiner states the only difference between the compound of the instant claims and the compound of Makarova *et al.* is a 2-thienyl group being attached to the ketone instead of an adamantyl group. The Applicants agree that one difference between the compound of the instant claims and Makarova *et al.* is the presence of a 2-thienyl group instead of an adamantyl group. However, the Examiner seems to have trivialized this difference, structurally a heteroaryl group (e.g. 2-thienyl) is very different than a tertiary aliphatic group (e.g. adamantyl). For example, simply based on the steric bulk of an adamantyl group, one

of skill in the art would expect the ketone adjacent to the adamantly group to have very different reduction properties compared to the ketone adjacent to the 2-thienyl group. Further, Makarova *et al.* does not disclose a β -aminovinyl ketone with *Z* stereochemistry. Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Syuzo Satake in which Mr. Satake attests that the *Z* isomer of *N*-methyl-3-oxo-3-(2-thienyl)propenamine has different physical properties than the *E* isomer. Thus, for the above reasons, the method of Claims 1 and 2 are not obvious in view of Makarova *et al.*

Moreover, the present invention is based, in part, on the unexpected discovery that reducing a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine) in the presence of a carboxylic acid provides an *N*-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine. The Examiner states that intermediate (*S*)-6 (*N*-methyl-3-hydroxy-3-(2-thienyl)propanamine) disclosed in Liu *et al.* provides motivation for applying the method of Makarova *et al.* to the (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine) as described in Claims 1 and 2. However, Liu *et al.* discloses a method of synthesizing (*S*)-6 (*N*-methyl-3-hydroxy-3-(2-thienyl)propanamine) from 3-chloro-1-(2-thienyl)-1-propanol by a completely unrelated method from the instant claims. If someone of ordinary skill in the art were motivated to synthesize *N*-methyl-3-hydroxy-3-(2-thienyl)propanamine, Liu *et al.* provides a reasonable synthesis of said compound. Accordingly, there is no need for one of skill in the art to go beyond the method disclosed Liu *et al.* to find an alternative method of synthesis. The Examiner has not explained why one of skill in the art would have any reason to go beyond the known method of Liu *et al.* to arrive at the method of Claims 1 and 2. Further, there is no discussion in Liu *et al.* that points to using (*Z*)-*N*-methyl-3-oxo-3-(2-thienyl)propenamine as an alternative intermediate in the synthesis of *N*-methyl-3-hydroxy-3-(2-thienyl)propanamine. Thus, for the above reasons, the method of Claims 1 and 2 are not obvious in view of Liu *et al.*

The combination of Liu *et al.* and Makarova *et al.* would not arrive at the claimed invention. Makarova *et al.* discloses a method of reducing compounds containing adamantly groups with sodium borohydride and Liu *et al.* discloses a method of forming *N*-methyl-3-hydroxy-3-(2-thienyl)propanamine by enzymatic methods. Applying the method of Makarova *et al.* to Liu *et al.* would render the key enzymatic transformation step of Liu *et al.* unsatisfactory for its intended purpose. If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to

make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). See MPEP 2143.01. Thus, Applicants submit, that for at least the preceding reasons, Claims 1 and 2 are not obvious over Liu *et al.* in view of Makarova *et al.* Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 4 and 5 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 4 and 5 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova *et al.* Examiner states that the prior art suggests the specific compound claimed. However, as explained below, this combination of references would not render the claimed invention as obvious. None of the cited references, even when combined would lead one of skill in the art to the (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine) of the instant claims.

The Examiner states that the adamantyl β -aminovinyl ketone of Makarova *et al.* combined with the teaching of Liu *et al.* suggests a (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine). However, Makarova *et al.* does not teach a β -aminovinyl ketone with a 2 thienyl group, rather, Makarova *et al.* discloses a β -aminovinyl ketone with an adamantyl group. Additionally, Liu *et al.* does not teach a β -aminovinyl ketone with a 2-thienyl group or any type of β -aminovinyl ketone.

As discussed previously, the Z isomer of N-methyl-3-oxo-3-(2-thienyl)propenamine has different physical properties than the E isomer. For example, the melting point of (Z)-N-methyl-3-oxo-3-(2-thienyl)propenamine is 20°C higher than (E)-N-methyl-3-oxo-3-(2-thienyl)propenamine. See Declaration page 3. Makarova *et al.* and Liu *et al.* do not teach, alone or in combination, 2-thienyl β -aminovinyl ketones with Z stereochemistry. For at least these reasons Claims 4 and 5 are not obvious over Liu *et al.* in view of Makarova *et al.*

The Examiner has suggested combing a moiety of the compounds of Liu *et al.* with a moiety of the compounds of Makarova *et al.* in a piecemeal fashion to arrive at the current invention. It is inappropriate to use the claims as a blueprint to modify the prior art to achieve the current invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner has maintained the previous rejection of Claims 4 and 5 under 35 U.S.C. § 103(a) as being obvious over Cassella Farbwerke *et al.* (CA 115:29157), Singh *et al.* (CA 115:29157) and/or Bogdanowicz-Szwed *et al.* (CA 136:118356) alone or in combination.

Specifically, the Examiner asserts that the references, which teach methyl analogs of compounds of Claims 4 and 5, render those claims obvious because methyl analogs of known compounds are allegedly considered to be obvious variants to one of skill in the art because of their close structural similarity.

The Examiner stated in a previous Office Action that Cassella Farbwerke *et al.* (CA 115:29157) teaches a process intermediate for preparing phenoxy-aminopropanols .. However, the compounds of Claims 4 and 5 could not be used to make the phenoxy-aminopropanols as disclosed in Cassella Farbwerke *et al.* (CA 115:29157). Thus one of skill in the art would have no motivation to arrive at the compounds of Claims 4 and 5 based on the disclosure of Cassella Farbwerke *et al.* (CA 115:29157). Applicant respectfully submits that the disclosure is not obvious over Cassella Farbwerke *et al.* (CA 115:29157) to one of ordinary skill in the art. In view that the cited reference fails to teach or suggest at least one limitation from Claims 4 and 5 and that there is insufficient motivation to modify the reference as suggested by the Examiner, Applicant respectfully submits that Claims 4 and 5 are in condition for allowance in view of Cassella Farbwerke *et al.* (CA 115:29157).

The Examiner stated in a previous Office Action that Singh *et al.* (CA 115:29157) teaches a methyl analog , that is, 3-amino-1-(2-thienyl)-2-buten-1-one of the instant compound, said methyl analog useful in the preparation of naphthyridones. However, it should be noted, the compounds of Claims 4 and 5 are positional isomers and not a methyl analog of 3-amino-1-(2-thienyl)-2-buten-1-one. Isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other. *Ex parte Mowry*, 91 USPQ 219 (Bd. App. 1950) (claimed cyclohexylstyrene not *prima facie* obvious over prior art isohexylstyrene). See MPEP § 2144.09. In order to arrive at the claimed compound from 3-amino-1-(2-thienyl)-2-buten-1-one one of skill in the art would have to remove a methyl group by breaking a carbon-carbon bond and add a methyl to the amine by forming a carbon-nitrogen bond. As discussed at the interview, this imagined chemical transformation takes two steps and is not a trivial transformation for one of ordinary or even extraordinary skill in the art. This is not a positional isomer as exemplified by the comparison of propyl alcohol and isopropyl alcohol where the methyl group is still bonded to a carbon atom but at a different position, it should be noted that the boiling point of propyl alcohol is 97 °C and the boiling point of isopropyl alcohol is 82 °C. The methyl to be isomerized

as suggested by the Examiner would be moved from a vinyl carbon position to an amine position. Again using propyl alcohol as an example, this type of isomerization would convert propyl alcohol to be methyl ethyl ether. As mentioned previously, the boiling point of propyl alcohol is 97 °C whereas the boiling point of methyl ethyl ether is 7.6 °C, as shown by this illustrative example, this type of change in positional isomer can provide a large change in physical properties in a compound. Further, Singh *et al.* (CA 115:29157) does not disclose the stereochemistry of the double bond. As discussed previously, the stereochemistry of the double bond has been shown to impart unexpected properties to the instant compounds. In view that the cited reference fails to teach or suggest at least one limitation from Claims 4 and 5 and that there is insufficient motivation to modify the reference as suggested by the Examiner, Applicant respectfully submits that Claims 4 and 5 are in condition for allowance in view of Singh *et al.* (CA 115:29157).

The Examiner stated in a previous Office Action that Bogdanowicz-Szwed *et al.* (CA 136:118356) teaches a methyl analog, that is, 3-dimethylamino-1-(2-thienyl)-2-buten-1-one, of the instant compound, which is a useful intermediate in the preparation of thiopyrans. However, it should be noted, 3-dimethylamino-1-(2-thienyl)-2-buten-1-one as disclosed in Bogdanowicz-Szwed *et al.* (CA 136:118356) has (*E*) stereochemistry. Thus, contrary to the Examiners assertion, the instant compounds are not merely a methyl analog of 3-dimethylamino-1-(2-thienyl)-2-buten-1-one as disclosed in Bogdanowicz-Szwed *et al.* (CA 136:118356). In order to arrive at the claimed compound from 3-amino-1-(2-thienyl)-2-buten-1-one one of skill in the art would have to remove a methyl group by breaking a carbon-nitrogen bond and isomerize the double bond. This imagined chemical transformation takes requires an isomerization step therefore it is not merely a methyl analog as the Examiner suggests. As discussed previously, the *Z* isomer of *N*-methyl-3-oxo-3-(2-thienyl)propenamine has different physical properties than the *E* isomer. The two step transformation suggested by the Examiner is not a trivial transformation for one of ordinary skill in the art. In view that the cited reference fails to teach or suggest at least one limitation from Claims 4 and 5 and that there is insufficient motivation to modify the reference as suggested by the Examiner, Applicant respectfully submits that Claims 4 and 5 are in condition for allowance in view of Bogdanowicz-Szwed *et al.* (CA 136:118356).

Further, the Examiner states in a previous Office Action that the *N*-dimethyl variant is the closest prior art method of record. A *prima facie* case of obviousness under 35 U.S.C. §103(a) can be rebutted upon a showing of a property not possessed by the prior art. *See, In re Papesch*,

315 F.2d 381 (CCPA, 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable."). While Applicants do not agree with the position taken by the PTO on the issue of obviousness, the Examiner concludes that, absent nonobvious or unexpected properties, the claimed compounds are considered to be obvious variants, wherein the results are predictable. As discussed above, the 3-dimethylamino-1-(2-thienyl)-2-buten-1-one as disclosed in Bogdanowicz-Szwed *et al.* (CA 136:118356) has (*E*) stereochemistry whereas the instant compounds have (*Z*) stereochemistry. Again, as discussed previously, the *Z* isomer of *N*-methyl-3-oxo-3-(2-thienyl)propenamine has a 20°C higher melting point than the (*E*) isomer. Thus, the known *Z* isomer compounds would not be expected to produce similar or expected results to the cited *Z* isomer compounds. In view that the cited reference fails to teach or suggest at least one limitation from Claims 4 and 5 and that there is insufficient motivation to modify the reference as suggested by the Examiner, Applicant respectfully submits that Claims 4 and 5 are in condition for allowance in view of Bogdanowicz-Szwed *et al.* (CA 136:118356).

Applicants submit that the claimed compounds of the present invention are quite different from the compounds disclosed in the three prior art references cited by the Examiner, Cassella Farbwerke *et al.* (CA 115:29157), Singh *et al.* (CA 115:29157) and Bogdanowicz-Szwed *et al.* (CA 136:118356). Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claim 6 under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 6 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova *et al.*, Wright *et al.* and Guseninov *et al.* Examiner states that one of skill in the art would be motivated by the teachings of Liu *et al.* and Markarova *et al.* to find the method of Claim 6 following the teachings Wright *et al.* and Guseninov *et al.* However, Wright *et al.* and Guseninov *et al.* do not teach a method of forming a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine). The example the Examiner has cited in Wright *et al.*, from Table I, includes an *N*-hydroxy benzyl amine moiety and a 4-chlorobenzene moiety not an *N*-monoalkyl amine moiety and 2-thienyl moiety as disclosed by Claim 6. An *N*-hydroxy benzyl amine moiety and a *N*-monoalkyl amine moiety are not structurally related. Also, 4-chlorobenzene moiety and a 2-thienyl moiety also are not structurally related. Further Claim 6 discloses a method using a salt form (e.g. sodium salt) of the β -ketoaldehyde to provide a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine. The Example the Examiner has cited in Guseninov *et al.* discloses formation

of an α -chloro- β -aminovinyl ketone where the ketone and the amino group have *E* stereochemistry in relation to each other. This is in contrast to the method of Claim 6 which does not include an α -chloro moiety and provides the *Z* isomer of *N*-methyl-3-oxo-3-(2-thienyl)propenamine. See Example 1 pages 1-2, Declaration under 37 C.F.R. § 1.132 by Syuzo Satake. Additionally, Guseninov *et al* does not disclose using a salt form (e.g. sodium salt) of the β -ketoaldehyde to provide a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Combining the teachings Wright *et al.* and Guseninov *et al.* would not provide the method of Claim 6. Neither Wright *et al.* nor Guseninov *et al.* disclose using a salt form (e.g. sodium salt) of the β -ketoaldehyde intermediate to provide a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine, thus, combining these references would not lead one of skill in the art to the instant claim using a salt form of the β -ketoaldehyde intermediate. Further, neither Wright *et al.* nor Guseninov *et al.* disclose (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine, thus for this additional reason, combining these references would not lead one of skill in the art to the instant claim. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 7 under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 7 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova *et al.*, Wright *et al.* and Guseninov *et al.* Examiner states that one of skill in the art would be motivated by the teachings of Liu *et al.* and Markarova *et al.* to find the method of Claim 7 following the teachings of Makarova *et al.*, Wright *et al.* and Guseninov *et al.* The Examiner states that Claim 7 is a combination of the processes of Claims 1 and 6. However, as discussed above, Makarova *et al.*, Wright *et al.* and Guseninov *et al.*, alone or in combination do not disclose the method of Claim 7. Specifically, Makarova *et al.*, Wright *et al.* and Guseninov *et al.* do not disclose using a salt form (e.g. sodium salt) of the β -ketoaldehyde to provide a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine. Further, Makarova *et al.*, Wright *et al.* and Guseninov *et al.* do not disclose a process for producing an *N*-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine by reducing a (*Z*)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine in the presence of a carboxylic acid. Establishing a *prima facie* obviousness requires a showing that each claim element is taught or suggested by the prior art. See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Thus, for at least these reasons, these references would not lead one of

skill in the art to the method of Claim 7. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 8 under 35 U.S.C. § 103(a)

The Examiner has rejected Claim 8 under 35 U.S.C. § 103(a) as being obvious over Liu *et al.* in view of Makarova *et al.*, Wright *et al.* and Guseninov *et al.* However, Makarova *et al.*, Wright *et al.* and Guseninov *et al.* do not disclose a process for producing an *N*-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine by reducing a (Z)-*N*-monoalkyl-3-oxo-3-(2-thienyl)propenamine) in the presence of a carboxylic acid and sodium borohydride or sodium cyanoborohydride. Establishing a *prima facie* obviousness requires a showing that each claim element is taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Thus, for at least this reason and the reasons set forth in reference to Claim 1, 6, and 7, these references would not lead one of skill in the art to the method of Claim 8. Accordingly, Applicants respectfully request withdrawal of the rejection.

Discussion of Obviousness-Type Double Patenting

In the Office Action, the Examiner provisionally rejected Claims 4 and 5 as being objected to under the judicially created doctrine of double patenting as being unpatentable over copending Application No. 11/989,100. In response, Applicant respectfully requests that the issue of obviousness-type double patenting be deferred until such time as either the present application or the copending application are in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history

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shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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